IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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| In re application of | : | **Confirmation No. 9413** |
| Shu KOBAYASHI | : | Attorney Docket No. 2006_1191A |
| Serial No. 10/587,078 | : | Group Art Unit 1621 |
| Filed October 20, 2006 | : | Examiner Lalitha Nagubandi |
| METHOD OF ENANTIOSELECTIVE NUCLEOPHILIC ADDITION REACTION OF ENAMIDE TO CARBONYL GROUP AND SYNTHESIS METHOD OF OPTICALLY ACTIVE α-HYDROXY-γ-KETO ACID ESTER AND HYDROXYDIKETONE | : | **Mail Stop: Amendment** |

THE COMMISSIONER IS AUTHORIZED TO CHARGE ANY DEFICIENCY IN THE FEE FOR THIS PAPER TO DEPOSIT ACCOUNT NO. 23-0975.

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**REQUEST FOR ACKNOWLEDGMENT OF RECEIPT OF PRIORITY DOCUMENTS**

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

The Office Action mailed August 31, 2007, does not acknowledge receipt of copies of the certified copies of Applicant's two Japanese priority applications. A copy of Form PCT/IB/304 is attached hereto, indicating that copies of both priority documents have been received by WIPO. It is expected that the USPTO has received copies of the priority documents from WIPO.

Accordingly, Applicant respectfully requests that the Examiner acknowledge receipt of the priority documents.

Respectfully submitted,

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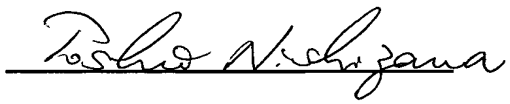
December 28, 2007

# CERTIFICATE

**I, Toshio NISHIZAWA, a citizen of JAPAN, residing at,** 4-3-14, KUDAN-KITA, CHIYODA-KU, **TOKYO, JAPAN hereby certify that I am conversant with the English and Japanese language, and I further certify that to the best of my knowledge and belief the foregoing is a true and correct English translation of the Japanese Patent Application No. JP 2004-016408, attached heteto.**

**Signed this 27th day of November, 2007**



**Toshio NISHIZAWA**

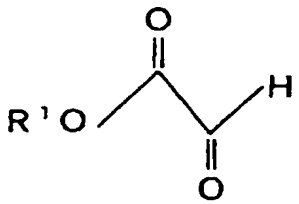
【Title of the document】 Scope of claims

【claim 1】 A method of an enantioselective nucleophilic addition reaction of enamide, which is a method of a nucleophilic addition reaction of an enamide compound accompanied by generation of a hydroxyl group (-OH) to an aldehyde group (-CHO) of an aldehyde compound, being characterized by allowing the reaction to be performed in the presence of a chiral copper catalyst.

【claim 2】 The method of the enantioselective nucleophilic addition reaction of enamide according to Claim 1, being characterized in that the chiral copper catalyst is constituted by a copper compound which is a salt of an organic or inorganic acid or a complex or composite of the salt, and a chiral diamine ligand.

【claim 3】 The method of the enantioselective nucleophilic addition reaction of enamide according to Claim 2, being characterized in that the chiral diamine ligand has an ethylene diamine structure as a portion thereof.

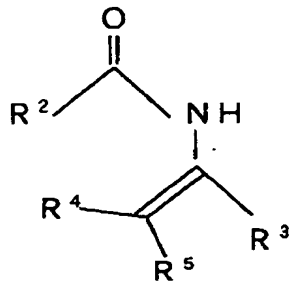
【claim 4】 A method of an enantioselective nucleophilic addition reaction of enamide, which is the method of the enantioselective nucleophilic addition reaction of enamide according to any one of Claims 1 to 3, being characterized in that the aldehyde compound is a glyoxylic acid ester represented by the following formula (1):




(1)

(wherein $R^1$ represents a hydrocarbon group which may have a substituent; and

the enamide compound is represented by the following formula (2):



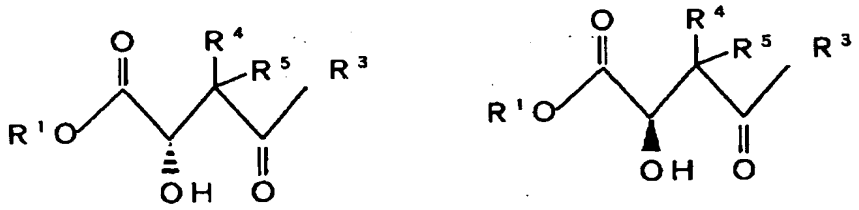
(2)

(wherein $R^2$ represents a hydrocarbon group which may have a substituent or a hydrocarbon group which may have a substituent to be bonded via an oxygen atom;

$R^3$ represents a hydrocarbon group which may have a substituent;

$R^4$ and $R^5$ may be same with or different from each other and each represent a hydrogen atom or a hydrocarbon group which may have a substituent, wherein at least one of them represents a hydrogen atom).

【claim 5】 A method for synthesizing an optically active α-hydroxy-γ-keto acid ester, being characterized in that, after the nucleophilic addition reaction according to Claim 4, an acid treatment is performed, to thereby generate a compound represented by at least one of the following formulae (3):

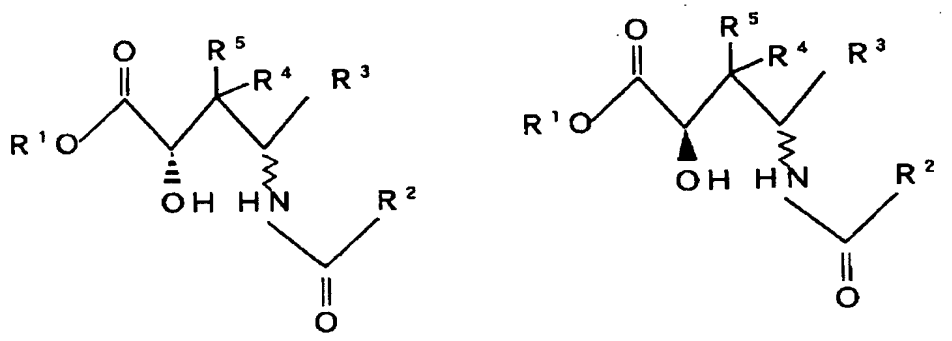


(3)

(wherein $R^1$, $R^3$, $R^4$ and $R^5$ each represent same article as described above).

【claim 6】 A method for synthesizing an optically active α-hydroxy-γ-amino acid

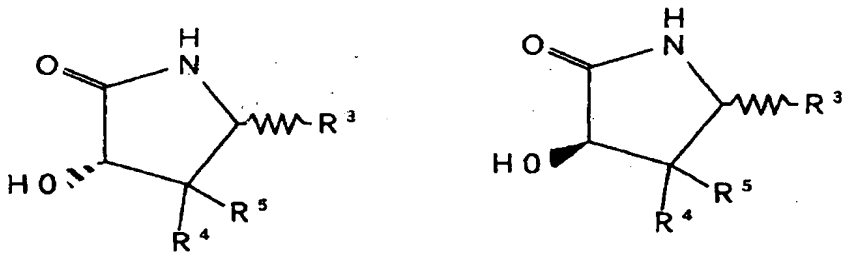
ester, being characterized in that, after the nucleophilic addition reaction according to Claim 4, a reduction treatment is performed, to thereby generate a compound represented by at least one of the following formulae (4):



(4)

(wherein $R^1$, $R^2$, $R^3$, $R^4$ and $R^5$ each represent same article as described above).

【claim 7】 A method for synthesizing optically active α-hydroxy-γ-lactams, being characterized in that, after a substituent ($R^2CO$-) on a γ-amino group of the optically active α-hydroxy-γ-amino acid ester synthesized by the method according to Claim 6 is removed, a cyclization reaction is performed, to thereby generate a compound represented by at least one of the following formulae (5):

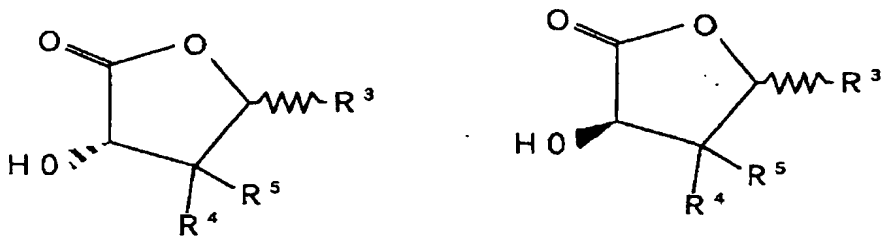


(5)

(wherein $R^3$, $R^4$ and $R^5$ each represent same article as described above).

【 claim 8 】 A method for synthesizing any one of optically active α-hydroxy-γ-lactones, being characterized in that the optically active α-hydroxy-γ-keto acid ester synthesized by the method according to Claim 5 is

subjected to a reduction reaction and, subsequently, to a cyclization reaction, to thereby generate a compound represented by at least one of the following formulae (6):



(6)

(wherein $R^3$, $R^4$ and $R^5$ each represent same article as described above).

【Title of the document】 Specification

【 Title of the invention 】 METHOD OF ENANTIOSELECTIVE NUCLEOPHILIC ADDITION REACTION OF ENAMIDE TO ALDEHYDE GROUP AND SYNTHESIS METHOD OF OPTICALLY ACTIVE α-HYDROXY-γ-KETO ACID ESTER

【Field of the invention】

The present invention relates to a method of an enantioselective nucleophilic addition reaction of enamide to an aldehyde group which enables an asymmetric synthesis of an optically active compound which is useful as a raw material or a synthesis intermediate for producing a pharmaceutical preparation, an agricultural chemical, a fragrance, a functional polymer or the like and, as an application thereof, a synthesis method of an optically active α-hydroxy-γ-keto acid ester or the like.

【Prior art and problems thereof】

Conventionally, a method of a nucleophilic addition reaction to an aldehyde group of an aldehyde compound or an imino group of an imine compound derived from the aldehyde compound has been studied and, in recent years, this nucleophilic addition reaction has drawn attention as a measure for efficiently and asymmetrically synthesizing an amino acid derivative, a hydroxycarboxylic acid or the like as a raw material or a synthesis intermediate for producing a pharmaceutical preparation, an agricultural chemical, a fragrance, a functional polymer or the like.

Under these circumstances, the present inventors have developed and disclosed a method for synthesizing an N-acylated amino acid derivative by a nucleophilic addition reaction to an N-acylimino ester compound by using a

polymer-carrying catalyst (Non-patent document 1) and, further, a method for enantioselectively synthesizing these compounds by using a chiral copper catalyst (Non-patent document 2-3).

【Non-patent document 1】Journal of Combinatorial Chemistry, 2001, Vol. 3, No. 5, 401 to 403

【Non-patent document 2】 Org. Lett. Vol. 4, No. 1, 2002, 143 to 145

【Non-patent document 3】 J. Am. Chem. Soc. Vol. 125, No. 9, 2003, 2507 to 2515

【Disclosure of invention】

【Problems to be solved by the invention】

However, the nucleophilic addition reaction on which the present inventors have studied is limited to such nucleophilic reactants as a silyl enol ether and an alkyl vinyl ether and, accordingly, a subject to which the nucleophilic addition reaction is applied and such application thereof have inevitably been restricted.

Then, under these circumstances, the present invention has an object of providing a method of an enantioselective nucleophilic addition reaction to an aldehyde group which enables an asymmetric synthesis of an α-hydroxy-γ-keto acid compound, an α-hydroxy-γ-amino acid compound or the like which is useful as a raw material or a synthesis intermediate for producing a pharmaceutical preparation, an agricultural chemical, a fragrance, a functional polymer or the like and, further, as an application thereof, a novel synthesis method of the α-hydroxy-γ-keto acid ester or the like.

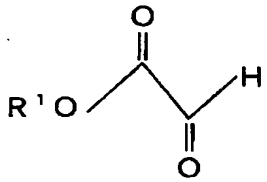
【Means for solving the problems】

In order to solve these problems, according to a first aspect of the present invention, there is provided a method of an enantioselective nucleophilic addition reaction of enamide which is a method of a nucleophilic addition reaction of an

enamide compound accompanied by generation of a hydroxyl group (-OH) to an aldehyde group (-CHO) of an aldehyde compound and which is characterized by allowing the reaction to be performed in the presence of a chiral copper catalyst.

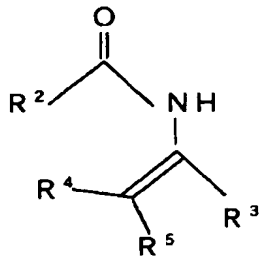
Then, with reference to the above-described method, according to a second aspect of the invention, there is provided the method of the enantioselective nucleophilic addition reaction of enamide which is characterized in that the chiral copper catalyst is constituted by a copper compound compound which is a salt of an organic or inorganic acid or a complex or composite of the salt, and a chiral diamine ligand and, according to a third aspect of the invention, there is provided the method of the enantioselective nucleophilic addition reaction of enamide which is characterized in that the chiral diamine ligand has an ethylene diamine structure as a portion thereof.

Further, according to a fourth aspect of the invention, with reference to the above-described method, there is provided the method of the enantioselective nucleophilic addition reaction of enamide which is characterized in that the aldehyde compound is a glyoxylic acid ester represented by the following formula (1):




(1)

(wherein $R^1$ represents a hydrocarbon group which may have a substituent; and the enamide compound is represented by the following formula (2):



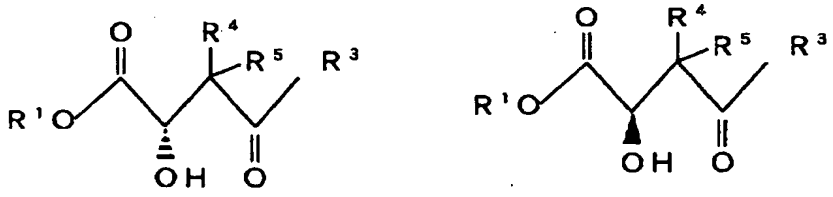
(2)

**(wherein $R^2$ represents a hydrocarbon group which may have a substituent or a hydrocarbon group which may have a substituent to be bonded via an oxygen atom;**

**$R^3$ represents a hydrocarbon group which may have a substituent;**

**$R^4$ and $R^5$ may be same with or different from each other and each represent a hydrogen atom or a hydrocarbon group which may have a substituent, wherein at least one of them represents a hydrogen atom).**

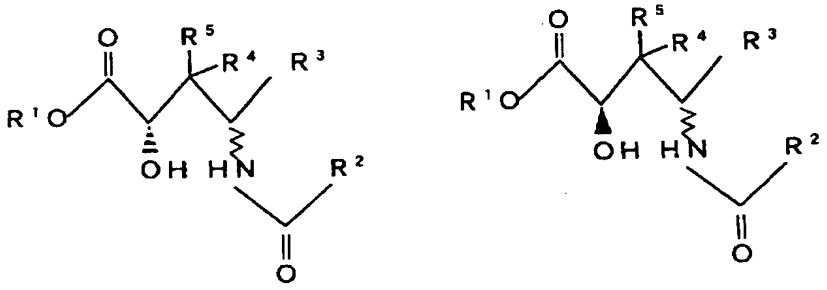
**According to a fifth aspect of the invention, there is provided a method for synthesizing an optically active α-hydroxy-γ-keto acid ester which is characterized in that, after the above-described nucleophilic addition reaction, an acid treatment is performed, to thereby generate a compound represented by at least one of the following formulae (3):**



(3)

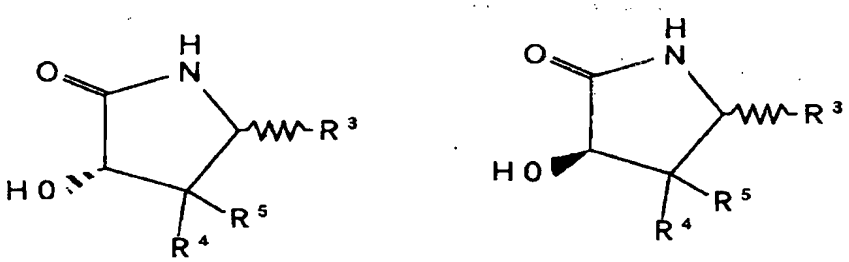
**(wherein $R^1$, $R^3$, $R^4$ and $R^5$ each represent same article as described above) and, according to an sixth aspect of the invention, there is provided a method for synthesizing an optically active α-hydroxy-γ-amino acid ester which is**

characterized in that, after the above-described nucleophilic addition reaction, a reduction treatment is performed, to thereby generate a compound represented by at least one of the following formulae (4):



(4)

(wherein $R^1$, $R^2$, $R^3$, $R^4$ and $R^5$ each represent same article as described above) and, further, according to a seventh aspect of the invention, there is provided a method for synthesizing any one of optically active α-hydroxy-γ-lactams which is characterized in that, after a substituent ($R^2CO$-) on a γ-amino group of the thus-synthesized optically active α-hydroxy-γ-amino acid ester is removed, a cyclization reaction is performed, to thereby generate a compound represented by at least one of the following formulae (5):

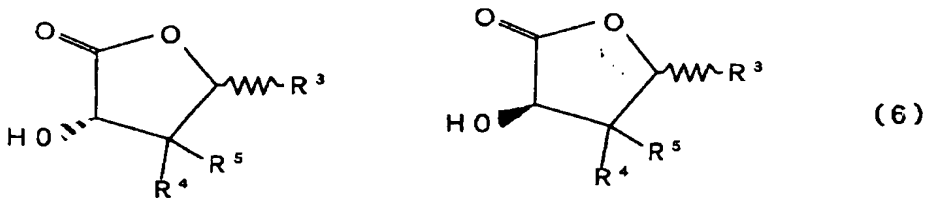


(5)

(wherein $R^3$, $R^4$ and $R^5$ each represent same article as described above).

Still further, according to a eighth aspect of the invention, there is provided a method for synthesizing any one of optically active

α-hydroxy-γ-lactones which is characterized in that the optically active α-hydroxy-γ-keto acid ester synthesized by the above-described fifth aspect of the invention is subjected to a reduction reaction and, subsequently, to a cyclization reaction, to thereby generate a compound represented by at least one of the following formulae (6):



(6)

(wherein $R^3$, $R^4$ and $R^5$ each represent same article as described above).

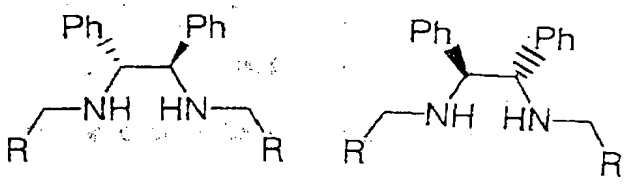
【Mode of practice of invention】

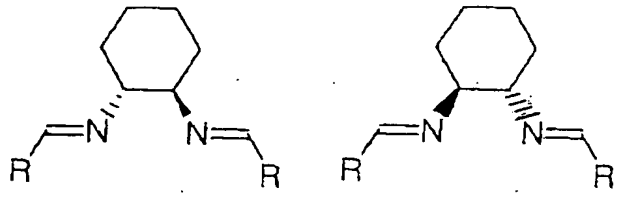
The present invention has characteristics as described above and is, further, described with reference to embodiments thereof.

In a method of an enantioselective nucleophilic addition reaction of enamide to an aldehyde group according to the invention, a chiral copper catalyst is used as a catalyst. As for the chiral copper catalyst on this occasion, various types of such chiral copper catalysts in each of which a copper atom is indispensable for a constitution thereof and to each of which a chiral organic molecular structure is attached are considered. Ordinarily, the chiral copper catalyst is constituted by a copper compound compound and a chiral organic compound and, more practically, from the standpoint of reaction yield and enantioselectivity, the chiral copper catalyst constituted by a copper compound and a chiral diamine ligand compound is favorably considered.

**The copper compound compound may be selected from among various types of salts, complex salts, organic metal compounds and the like as a monovalent or bivalent copper compound and, among other things, a salt with an organic or inorganic acid, a complex or organic composite of the salt is favorably mentioned. Among these compounds, a salt with a strong acid, for example, a salt of (per)fluoroalkyl sulfonic acid, perchloric acid or sulfonic acid, a complex or an organic composite of the salt is favorably illustrated. For example, $Cu(OTf)_2$, $CuClO_4$, and $CuClO_4 \cdot 4CH_3CN$ are mentioned.**

**As for the chiral diamine ligand as a counterpart, an article having an ethylene diamine structure in a molecular constitution as a portion thereof is favorably used. On this occasion, an amino group may contain an imine bond. For example, as representatives, various types represented by the following formulae are illustrated:**



On this occasion, R in the formulae represents a hydrocarbon group which may have a substituent. The hydrocarbon group may be any one of various types in a chain state or a cyclic state and may have, as a substituent, a halogen atom, a hydrocarbon group of an alkyl group or the like, an alkoxy group or the like. Further, Ph (phenyl group) and a cyclohexyl group in the formulae may each have a substituent.

With reference to the chiral copper catalyst as described above according to the invention, a complex may previously be prepared by using a copper compound and a chiral organic molecule and, then, used as a catalyst, or the copper compound and the chiral organic molecule may be mixed with each other in a reaction system and, then, used. As far as a ratio in use as a catalyst is concerned, the copper compound or the complex of the copper compound and the chiral organic molecule is used at a rate of ordinarily from about 0.5 to about 30% by mol against the aldehyde compound.

The aldehyde compound to be used in the reaction may have any type of structure of an aliphatic, alicyclic, aromatic or a heterocyclic aldehyde compound or the like which may have a substituent, so long as it does not interfere with the nucleophilic addition reaction according to the present invention. For example, as for the aldehyde compound, a glyoxylic acid ester represented by the formula (1) is illustrated. This article has an ester bond portion and reference mark $R^1$ in the formula represents a hydrocarbon group which may have a substituent. The hydrocarbon group may be any one of various types of hydrocarbon groups, for example, a chain or an alicyclic hydrocarbon group, an aromatic hydrocarbon group and mixtures thereof. As for such substituents, so long as they do not interfere with the nucleophilic addition reaction, the hydrocarbon group may

appropriately have any one of various types of substituents such as a hydrocarbon group such as an alkyl group, an alkoxy group, a sulfide group, a cyano group, a nitro group, and an ester group.

The enamide compound as a counterpart can, for example, be represented by the above-described formula (2). As for characteristics thereof, it has an amide bond or a carbamate bond. As for reference marks in the formula, $R^2$ represents a hydrocarbon group which may have a substituent or a hydrocarbon group which may have a substituent to be bonded via an oxygen atom; $R^3$ represents a hydrocarbon group which may have a substituent; and $R^4$ and $R^5$ may be same with or different from each other and each represent a hydrogen atom or a hydrocarbon group which may have a substituent, in which at least one of them represents a hydrogen atom.

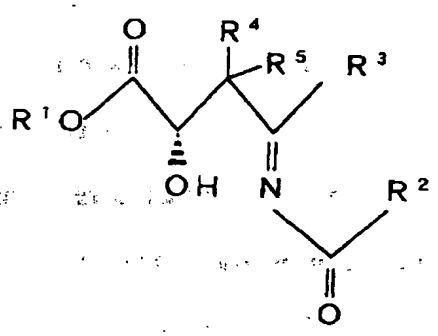
The hydrocarbon group may be any one of various types of hydrocarbon groups in a same manner as described above, for example, an aliphatic hydrocarbon group, an alicyclic hydrocarbon group, an aromatic hydrocarbon group and mixtures thereof. As for such substituents, various types of substituents such as a hydrocarbon group such as an alkyl group, a halogen atom, an alkoxy group, a sulfide group, a cyano group, a nitro group, and an ester group are appropriately be considered.

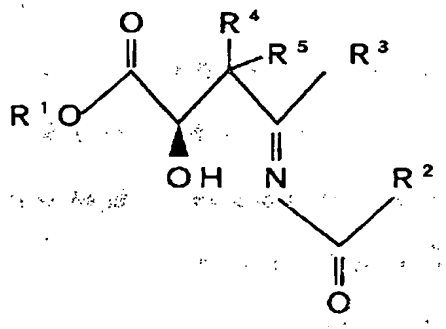
Further, as for reference mark $R^2$, a hydrocarbon group which is bonded via an oxygen atom such as –OEt, -O$^t$Bu, or –OBn is appropriately illustrated. As for reference mark $R^3$, an article having a substituent such as a phenyl group, a naphthyl group, or any one of these groups each having a substituent such as a halogen atom, an alkyl group, or an alkoxy group is favorably illustrated.

In the nucleophilic addition reaction of the enamide compound to the

aldehyde group (-CHO) of the glyoxylic acid ester, an appropriate organic solvent, for example, a halogenated hydrocarbon, any one of nitriles such as acetonitrile, or any one of ethers such as THF may be used and, in a reaction temperature, a range of from about -20°C to about 40°C can appropriately be adopted. A ratio of the aldehyde compound to the enamide compound to be used in an atmosphere of the air or in an inert atmosphere can appropriately be set to be in the range of from about 0.1 to about 10 in terms of a molar ratio.

In the nucleophilic addition reaction of the enamide compound, when a reaction between the glyoxylic acid ester represented by the above-described formula (1) and the enamide compound represented by the above-described formula (2) is taken as an example, an optically active α-hydroxy-γ-imino acid ester represented by at least one of the following formulae is enantioselectively generated:





Then, particularly, when enecarbamate is used as a type of the enamide compound, a high stereoselectivity can also be realized. A syn-adduct and an anti-adduct can be obtained from a Z-body and an E-body at high diastereoselectivity and high enantioselectivity, respectively. By either without isolating or isolating the above-described imino acid ester compound, an acid treatment, for example, an acid treatment by using an aqueous solution of HCl,

HBr or the like is performed, to thereby obtain the optically active α-hydroxy-γ-keto acid ester represented by the above-described formula (3) at high yield and with excellent enantioselectivity.

Further, on the other hand, without performing the acid treatment but performing a reduction treatment, the optically active α-hydroxy-γ-amino acid ester represented by the above-described formula (4) can be obtained at high yield and with excellent enantioselectivity in a same manner as described above. The reduction treatment on this occasion can use, for example, a boron reducing agent compound such as $Et_2BOMe$-$NaBH_4$, any one of other metal hydrides or a metallic hydrogen complex compound. Then, the thus-generated optically active α-hydroxy-γ-amino acid ester is subjected to a cyclization reaction to remove an acyl group on a γ-amino group therefrom (freeig from protection), to thereby being favorably converted into any one of optically active α-hydroxy-γ-lactams represented by the formula (5). For example, when the acyl group is a benzyloxycarbonyl group, protection freeing-cyclization reaction can be performed by catalytic hydrogen reduction.

Further, in the present invention, it is possible to synthesize the optically active α-hydroxy-γ-lactams as represented by the above-described formula (6) by subject the optically active α-hydroxy-γ-keto acid ester as described above firstly to a reduction reaction and, then, to a cyclization reaction.

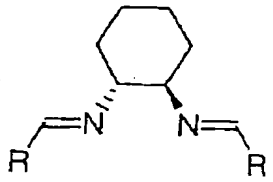
Hereinafter, the present invention is described in detail with reference to embodiments.

It goes without saying that the present invention is not limited to these embodiments.

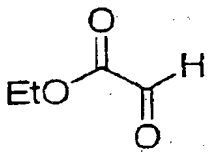
【Example】

**<Example 1>**

**In the formula described below, a $CH_2Cl_2$ (1.5 ml) solution of chiral diamine ligand (9.9 mg, 0.022 mmol) in which R represents 4-$BrC_6H_4$ is added to $CuClO_4 \cdot 4CH_3CN$ (6.5 mg, 0.020 mmol) in an argon atmosphere and the resultant excellent yellow solution was stirred for 8 hours or more and, then, cooled to 0°C.**




**Next, into the resultant mixed solution, a $CH_2Cl_2$ (0.8 ml) solution of ethyl glyoxylate (100 μl, 0.40 mmol) represented by the formula described below was added and, further, a $CH_2Cl_2$ (0.8 ml) solution of enamide (0.20 mmol) represented by the formula (2) as shown in Table 1 was added.**




**The resultant reaction mixed solution was stirred for one hour at 0°C and, then, added with a saturated aqueous solution of $NaHCO_3$, to thereby terminate a reaction. Thereafter, the resultant reaction mixed solution was allowed to have room temperature and, then, subjected to extraction by using $CH_2Cl_2$. The resultant organic phase was rinsed and, then, dried. After a solvent was evaporated, a residue was dissolved in EtOH (3.0 ml), added with a 48% aqueous HBr solution (0.3 ml) and, then, stirred for 1.5 minute at room temperature.**

**The resultant reaction mixture was subjected to extraction by using $CH_2Cl_2$. The resultant organic phase was rinsed and, then, dried. After a**

solvent was evaporated, a crude product was obtained. This crude product was purified by using silica gel chromatography.

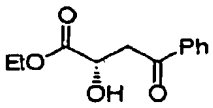
In Table 1, the reaction yield and ee (%) in accordance with the type of enamide are shown. On this occasion, the ee (%) was determined by an HPLC analysis.

Table 1

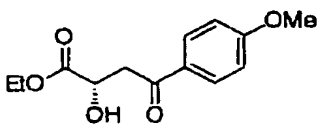
| No. | $R^2$ | $R^3$ | $R^4$, $R^5$ | Yield (%) | ee (%) |
|---|---|---|---|---|---|
| 1-1 | BnO | Ph | H, H | 93 | 97 |
| 1-2 | BnO | 4-MeO-Ph | H, H | 94 | 93 |
| 1-3 | BnO | 4-Cl-Ph | H, H | 97 | 97 |
| 1-4 | BnO | 4-Me-Ph | H, H | quantum | 96 |
| 1-5 | BnO | 2-naphthyl | H, H | 91 | 96 |

Identification values of products in the case of Nos. 1-1 to 1-5 are shown below.

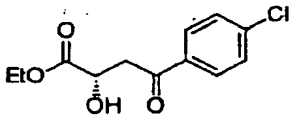
## Table 2



**(2*S*)-2-Hydroxy-4-oxo-4-phenyl-butyric acid ethyl ester:** $^1$H NMR ($CDCl_3$) δ = 1.27 (t, 3H, *J* = 7.1 Hz), 3.29 (brs, 1H), 3.44 (dd, 1H, *J* = 6.1, 17.6 Hz), 3.52 (dd, 1H, *J* = 3.9, 17.6 Hz), 4.25 (q, 2H, *J* = 7.1 Hz), 4.61-4.67 (m, 1H), 7.44-7.50 (m, 2H), 7.54-7.60 (m, 1H), 7.92-7.98 (m, 2H); $^{13}$C NMR ($CDCl_3$) δ = 14.0, 42.1, 61.8, 67.1, 128.1, 128.6, 133.5, 136.4, 173.7, 197.5. IR (neat) 3475, 3063, 2983, 1737, 1687, 1597, 1580, 1449, 1368, 1213, 1098, 1045, 860, 759, 690, 582, 499 cm$^{-1}$; HRMS (FAB); Exact mass calcd for $C_{12}H_{15}O_4$ $[M+H]^+$, 223.0970. Found 223.0972.; HPLC, Daicel Chiralcel ADH, hexane/$^i$PrOH = 4/1, flow rate = 0.5 mL/min : $t_R$ = 19.9 min (*S*), $t_R$ = 22.2 min (*R*).

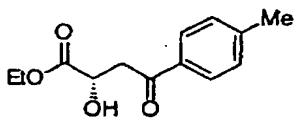


**(2*S*)-2-Hydroxy-4-(4-methoxy-phenyl)-4-oxo-butyric acid ethyl ester:** $^1$H NMR ($CDCl_3$) δ = 1.28 (t, 3H, *J* = 7.1 Hz), 3.41 (dd, 1H, *J* = 5.9, 17.4 Hz), 3.48 (dd, 1H, *J* = 4.0, 17.4 Hz), 3.48 (brd, 1H, *J* = 6.8 Hz), 3.87 (s, 3H), 4.26 (q, 2H, *J* = 7.1 Hz), 4.60-4.70 (m, 1H), 6.91-6.97 (m, 2H), 7.90-7.97 (m, 2H); $^{13}$C NMR ($CDCl_3$) δ = 14.0, 41.7, 55.4, 61.7, 67.3, 113.8, 129.5, 130.4, 163.8, 173.8, 196.1. IR (neat) 3483, 2979, 2841, 1739, 1677, 1600, 1575, 1512, 1465, 1421, 1368, 1265, 1172, 1099, 1027, 988, 895, 834, 737, 579 cm$^{-1}$; HRMS (FAB); Exact mass calcd for $C_{13}H_{17}O_5$ $[M+H]^+$, 253.1076. Found 253.1097.; HPLC, Daicel Chiralcel ADH, hexane/$^i$PrOH = 4/1, flow rate = 0.4 mL/min : $t_R$ = 43.1 min (*S*), $t_R$ = 45.7 min (*R*).

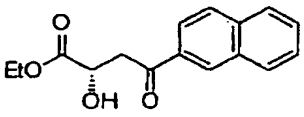


**(2*S*)-4-(4-Chloro-phenyl)-2-hydroxy-4-oxo-butyric acid ethyl ester:** $^1$H NMR ($CDCl_3$) δ = 1.28 (t, 3H, *J* = 7.1 Hz), 3.42 (dd, 1H, *J* = 6.1, 17.3 Hz), 3.49 (dd, 1H, *J* = 3.9, 17.3 Hz), 3.41-3.47 (brd, 1H), 4.26 (q, 2H, *J* = 7.1 Hz), 4.62-4.70 (m, 1H), 7.42-7.48 (m, 2H), 7.86-7.93 (m, 2H); $^{13}$C NMR ($CDCl_3$) δ = 14.1, 42.2, 62.0, 67.1, 129.0, 129.6, 134.8, 140.1, 173.7, 196.3. IR (neat) 3480, 2982, 1739, 1684, 1590, 1573, 1402, 1213, 1093, 1045, 820, 531 cm$^{-1}$; HRMS (FAB); Exact mass calcd for $C_{12}H_{14}ClO_4$ $[M+H]^+$, 257.0580. Found 257.0584.; HPLC, Daicel Chiralcel ADH, hexane/$^i$PrOH = 4/1, flow rate = 0.5 mL/min : $t_R$ = 24.2 min (*S*), $t_R$ = 26.5 min (*R*).

## Table 3



**(2*S*)-2-Hydroxy-4-oxo-4-*p*-tolyl-butyric acid ethyl ester:** $^1$H NMR ($CDCl_3$) δ = 1.28 (t, 3H, *J* = 7.1 Hz), 2.41 (s, 3H), 3.44 (dd, 1H, *J* = 5.9, 17.4 Hz), 3.51 (dd, 1H, *J* = 4.0, 17.4 Hz), 3.45-3.55 (brs, 1H), 4.26 (q, 2H, *J* = 7.1 Hz), 4.66 (dt, 1H, *J* = 4.2, 5.5 Hz), 7.26 (apparent d, 2H, *J* = 8.0 Hz), 7.85 (apparent d, 2H, *J* = 8.2 Hz); $^{13}$C NMR ($CDCl_3$) δ = 14.0, 21.6, 42.0, 61.7, 67.2, 128.2, 129.3, 133.9, 144.4, 173.7, 197.1. IR (neat) 3483, 2981, 1742, 1682, 1606, 1405, 1365, 1212, 1098, 1044, 813, 578 $cm^{-1}$; HRMS (FAB); Exact mass calcd for $C_{13}H_{17}O_4$ $[M+H]^+$, 237.1127. Found 237.1120.; HPLC, Daicel Chiralcel ADH, hexane/$^i$PrOH = 4/1, flow rate = 0.3 mL/min : $t_R$ = 36.1 min (*S*), $t_R$ = 38.2 min (*R*).



**(2*S*)-2-Hydroxy-4-naphthalen-2-yl-4-oxo-butyric acid ethyl ester:** $^1$H NMR ($CDCl_3$) δ = 1.28 (t, 3H, *J* = 7.1 Hz), 3.52 (d, 1H, *J* = 5.9 Hz), 3.59 (dd, 1H, *J* = 6.1, 17.3 Hz), 3.66 (dd, 1H, *J* = 3.9, 17.3 Hz), 4.28 (q, 2H, *J* = 7.1 Hz), 4.73 (dt, 1H, *J* = 4.2, 5.4 Hz), 7.50-7.65 (m, 2H), 7.82-8.20 (m, 4H), 8.45 (s, 1H); $^{13}$C NMR ($CDCl_3$) δ = 14.1, 42.3, 61.9, 67.3, 123.6, 126.9, 127.8, 128.6, 128.8, 129.6, 130.2, 132.4, 133.8, 135.8, 173.9, 197.5. IR (neat) 3481, 3058, 2982, 1741, 1681, 1627, 1469, 1369, 1209, 1097, 1045, 859, 824, 749, 477 $cm^{-1}$; HRMS (FAB); Exact mass calcd for $C_{16}H_{17}O_4$ $[M+H]^+$, 273.1127. Found 273.1125.; HPLC, Daicel Chiralcel ADH, hexane/$^i$PrOH = 4/1, flow rate = 0.5 mL/min : $t_R$ = 27.0 min (*S*), $t_R$ = 30.4 min (*R*).

**<Example 2>**

**A reaction was performed in a same manner as in Example 1 No.1-1, except for using a chiral diamine ligand in which R represents Ph (phenyl group), the results in which the yield was 99 % and ee (%) of a reaction product was 93 were obtained.**

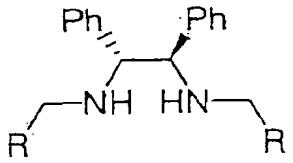
**<Example 3>**

**A reaction was performed in a same manner as in Example 2 except that $Cu(OTf)_2$ was used in place of the copper compound, the results in which the yield was 65 % and ee (%) of a reaction product was 70 were obtained.**

**An absolute configuration of the product was R.**

**<Example 4>**

**A reaction was performed in a same manner as in Example 3, except for using a chiral diamine ligand represented by the following formula in which R represents 1-naphthyl group, the results in which the yield was 93 % and ee (%) of a reaction product was 55 were obtained.**




**An absolute configuration of the product was R.**

**<Example 5>**

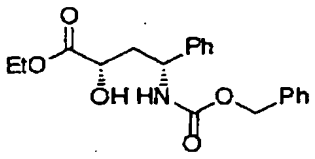
**A treatment as described below was performed in place of the acid treatment by using the aqueous HBr solution in Example 1.**

**Namely, the residue was added with a mixed solution of THF (2.0 ml) and MeOH (0.5 ml) and, then, cooled to -78°C and, thereafter, added with $Et_2BOMe$ (79 μl, 0.6 mmol) and, subsequently, stirred for 15 minutes. The resultant mixed solution was added with $NaBH_4$ (22.7 mg, 0.6 mmol) and, then, cooled to -78°C and stirred for 2 hours at this temperature.**

**Then, a reaction was terminated by being added with AcOH (0.3 μl) and, then, allowed to have room temperature.**

**The compound described below was obtained in an amount of 46.5 mg at a yield of 65%. A ratio of syn/anti was 94/6.**

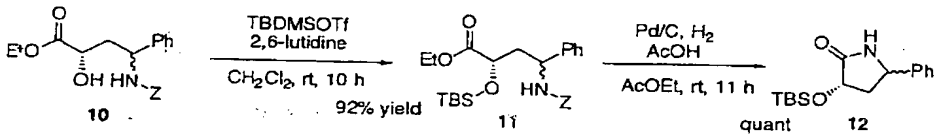
## Table 4



**4-Benzyloxycarbonylamino-2-hydroxy-4-phenyl-butyric acid ethyl ester: (10, *syn/anti* = 94/6)**: $^1$H NMR ($CDCl_3$) δ = 1.23 (t, 3H x 19/20, *J* = 7.1 Hz), 1.25 (t, 3H x 1/20, *J* = 7.0 Hz), 1.95-2.40 (m, 2H), 3.33 (brs, 1H x 19/20), 3.51 (brs, 1H x 1/20), 4.00-4.40 (m, 3H), 4.85-5.20 (m, 3H), 5.52 (d, 1H x 19/20, *J* = 7.3 Hz), 5.96 (d, 1H x 1/20, *J* = 8.2 Hz), 7.00-7.60 (m, 10H); $^{13}$C NMR ($CDCl_3$) ***syn***: δ = 14.1, 40.3, 52.6, 61.8, 66.8, 68.4, 126.4, 127.6, 128.1, 128.4, 128.7, 136.3, 141.4, 155.7, 174.4; ***anti***: (distinguishable peak) 40.2, 52.4, 67.8, 126.2, 127.4, 141.1, 156.0, 174.3; LRMS (FAB) *m/z* = 358 ($M+H^+$)

**<Example 6>**

**In accordance with the following reaction formulae, γ-lactams (12) were synthesized from the product obtained in Example 5:**




**(wherein Z represents benzyloxycarbonyl group)**

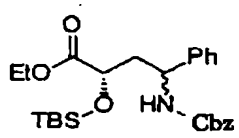
**1) A $CH_2Cl_2$ (0.6 ml) solution of the above-described product (10) (31.3 mg, 0.088 mmol) was added with a $CH_2Cl_2$ (0.2 ml) solution of 2.6-lutidine (12.0 mg, 0.114 mmol) and a $CH_2Cl_2$ solution of tert-butyl dimethyl silyl trifluoromethane sulfonate: TBDMSOTf (27.8 mg, 0.105 mmol) at a temperature of 0°C.**

**A reaction mixture was stirred for 10 hours at room temperature.**

**After the resultant reaction mixture was added with water, it was subjected to extraction by using $CH_2Cl_2$ and, then, the resultant organic phase was rinsed and, then, dried and, thereafter, a solvent therein was evaporated. The**

**resultant crude product was purified by using silica gel chromatography, to thereby obtain 37.9 mg (with a yield of 92%) of a next compound (11).**

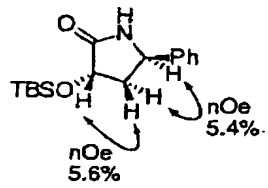
**Table 5**



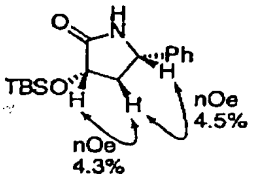

**4-Benzyloxycarbonylamino-2-(*tert*-butyl-dimethyl-silanyloxy)-4-phenyl-butyric acid ethyl ester (11, diastereomer mixture):** $^1$H NMR ($CDCl_3$) δ = ***syn*:** –0.03 (s, 3H), 0.02 (s, 3H), 0.90 (s, 9H), 1.15-1.27 (m, 3H), 2.00-2.35 (m, 2H), 3.90-4.30 (m, 3H), 4.80-5.15 (m, 3H), 5.50 (brs, 1H), 7.15-7.40 (m, 10 H); ***anti*:** (distinguishable peak) δ = –0.02 (s, 3H), 0.03 (s, 3H), 5.62 (brd, 1H, $J$ = 7.7 Hz); $^{13}$C NMR ($CDCl_3$) ***syn*:** δ = –5.4, –5.0, 14.0, 18.1, 25.7, 41.0, 52.9, 61.0, 66.6, 70.3, 126.4, 127.4, 128.0, 128.1, 128.4, 128.6, 136.4, 141.8, 155.3, 173.2; ***anti*:** (distinguishable peak) –5.0, 14.1, 41.8, 52.3, 69.8, 126.0, 127.3, 128.6, 142.2, 155.6, 173.1; IR (neat) 3343, 2940, 1720, 1518, 1254, 1131, 1038, 839, 781, 699cm$^{-1}$; HRMS (FAB); Exact mass calcd for $C_{26}H_{38}NO_5Si$ $[M+H]^+$, 472.2519. Found 472.2508.

**2) An AcOEt (2.0 ml) solution of the above-described product (11) (21.4 mg, 0.454 mmol) was added with AcOH (16.8 mg, 0.0272 mmol) and a 5% Pd/C (9.7 mg, 10% by mol) at room temperature. After an argon gas in the atmosphere of the resultant mixture was replaced with an $H_2$ gas, the mixture was stirred for 11 hours, to thereby obtain a next compound (12) (13.4 mg, quantitative yield). A diastereomer (12) can be separated by using silica gel chromatography.**

## Table 6




**(3*S*, 5*R*)-3-(*tert*-Butyl-dimethyl-silanyloxy)-5-phenyl-pyrrolidin-2-one (12-major):** $^1$H NMR ($CDCl_3$) $\delta$ = 0.14 (s, 3H), 0.16 (s, 3H), 0.91 (s, 9H), 2.21 (ddd, 1H, $J$ = 5.1, 7.1, 13.2 Hz), 2.46 (ddd, 1H, $J$ = 5.1, 7.5, 13.2 Hz), 4.38 (dd, 1H, $J$ = 5.1, 7.1 Hz), 4.83 (dd, 1H, $J$ = 5.0, 7.5 Hz), 6.02 (brs, 1H), 7.20-7.43 (m, 5H); $^{13}$C NMR ($CDCl_3$) $\delta$ = –5.1, –4.5, 18.3, 25.8, 41.5, 55.1, 69.9, 125.5, 127.9, 129.0, 142.1, 176.3; IR (neat) 3226, 2927, 2892, 2855, 1715, 1496, 1471, 1331, 1253, 1151, 1091, 1028, 963, 880, 839, 780, 699 cm$^{-1}$; HRMS (FAB); Exact mass calcd for $C_{16}H_{26}NO_2Si$ $[M+H]^+$, 292.1733. Found 292.1733.;




**(3*S*, 5*S*)-3-(*tert*-Butyl-dimethyl-silanyloxy)-5-phenyl-pyrrolidin-2-one (12-minor):** $^1$H NMR ($CDCl_3$) $\delta$ = 0.15 (s, 3H), 0.20 (s, 3H), 0.91 (s, 9H), 1.94 (dt, 1H, $J$ = 9.2, 12.6 Hz), 2.75-2.87 (m, 1H), 4.42 (dd, 1H, $J$ = 7.9, 9.2 Hz), 4.53 (dd, 1H, $J$ = 6.2, 8.6 Hz), 5.76 (brs, 1H), 7.30-7.40 (m, 5H); $^{13}$C NMR ($CDCl_3$) $\delta$ = –5.1, –4.5, 118.3, 25.8, 42.0, 53.9, 70.8, 126.1, 128.2, 128.9, 176.0; IR (neat) 3220, 2936, 2858, 2359, 1717, 1463, 1330, 1247, 1151, 882, 838, 781, 698 cm$^{-1}$; HRMS (FAB); Exact mass calcd for $C_{16}H_{26}NO_2Si$ $[M+H]^+$, 292.1733. Found 292.1736.;

**<Example 7>**

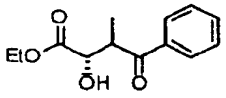
**A reaction was performed in a same manner as in Example 1 except that various types of enecarbamates shown in Table 7 as enamides represented by the above-described formula (2) were used. In Table 1, yield (%), a syn/anti ratio, and ee (%) of a reaction product are shown. In Table 8, identification values of 7-1/7-2, 7-3/7-4, 7-5/7-6 and 7-7/7-8 of the reaction products are shown.**

**From the results of this reaction, it was confirmed that an anti-adduct and a syn-adduct were obtained from an E-body and a Z-body at high diastereoselectivity and high enantioselectivity, respectively.**

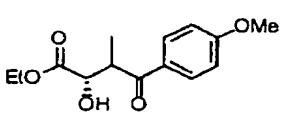
Table 7

| No. | $R^2$ | $R^3$ | $R^4$・$R^5$ | 収率 (%) | Syn/anti | ee (%) |
|---|---|---|---|---|---|---|
| 7－1 | BnO | Ph | Me, H (E) | 83 | 1／99 | 98 |
| 7－2 | BnO | Ph | H, Me (Z) | 82 | 98／2 | 98 |
| 7－3 | BnO | 4－MeO－Ph | Me, H (E) | 96 | 2／98 | 98 |
| 7－4 | BnO | 4－MeO－Ph | H, Me (Z) | 97 | 98／2 | 98 |
| 7－5 | EtO | 4－MeO－Ph | Me, H (E) | 82 | 3／97 | 96 |
| 7－6 | EtO | 4－MeO－Ph | H, Me (Z) | 96 | 99／1 | 98 |
| 7－7 | BnO | 4－Cl－$C_6H_4$ | Me, H (E) | 85 | 2／98 | 98 |
| 7－8 | BnO | 4－Cl－$C_6H_4$ | H, Me (Z) | 79 | 99／1 | 98 |

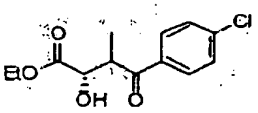
## Table 8



**(2*S*)-2-Hydroxy-3-methyl-4-oxo-4-phenyl-butyric acid ethyl ester ( *syn/anti* mixture):** $^1$H NMR ***syn*** ($CDCl_3$) δ = 1.26 (t, 3H, *J* = 7.0 Hz), 1.29 (d, 3H, *J* = 7.0 Hz), 3.28 (br, 1H), 3.93 (dq, 1H, *J* = 4.2, 7.0 Hz), 4.25 (q, 2H, *J* = 7.0 Hz), 4.58 (d, 1H, *J* = 4.2 Hz), 7.40-7.65 (m, 3H), 7.90-8.05 (m, 2H); ***anti*** ($CDCl_3$) δ = 1.20 (t, 3H, *J* = 7.1 Hz), 1.36 (d, 3H, *J* = 7.3 Hz), 3.61 (d, 1H, *J* = 8.3 Hz), 3.98 (dq, 1H, *J* = 4.6, 7.1 Hz), 4.10-4.25 (m, 2H), 4.39 (dd, 1H, *J* = 4.6, 8.3 Hz), 7.40-7.65 (m, 3H); $^{13}$C NMR ***syn*** ($CDCl_3$) δ = 12.1, 14.0, 44.3, 61.9, 71.6, 128.4, 128.7, 133.3, 135.7, 173.1, 201.6; ***anti*** ($CDCl_3$) δ = 14.0, 14.1, 44.0, 61.5, 73.1, 128.3, 128.7, 133.4, 135.9, 173.1; IR (neat) ***syn*** 3480, 3063, 2978, 2936, 1734, 1678, 1596, 1579, 1449, 1369, 1217, 1133, 1062, 1023, 1001, 975, 952, 862, 794, 708; ***anti*** 3481, 3059, 2981, 2941, 1738, 1685, 1588, 1454, 1372, 1255, 1209, 1144, 1092, 1024, 973, 701 cm$^{-1}$; HRMS (FAB); Exact mass calcd for $C_{13}H_{17}O_4$ $[M+H]^+$, 237.1127. Found 237.1118.; HPLC, Daicel Chiralcel AS + ADH + AD, hexane/$^i$PrOH = 4/1, flow rate = 0.5 mL/min : $t_R$ = 46.7 min (2*S*, 3*S*), $t_R$ = 50.6 min (2*R*, 3*R*), $t_R$ = 54.3 min (2*S*, 3*R*), $t_R$ = 61.9 min (2*R*, 3*S*).



**(2*S*)-2-Hydroxy-4-(4-methoxy-phenyl)-3-methyl-4-oxo-butyric acid ethyl ester ( *syn/anti* mixture):** $^1$H NMR ***syn*** ($CDCl_3$) δ = 1.28 (t, 3H, *J* = 7.1 Hz), 1.29 (d, 3H, *J* = 7.1 Hz), 3.35 (br, 1H), 3.84-3.96 (m, 4H), 4.27 (q, 2H, *J* = 7.1 Hz), 4.58 (t, 1H, *J* = 4.2 Hz), 6.96 (apparent d, 2H, *J* = 9.0 Hz), 7.30-7.45 (m, 5H), 7.95 (apparent d, 2H, *J* = 8.8 Hz); ***anti*** ($CDCl_3$) δ = 1.19 (t, 3H, *J* = 7.1 Hz), 1.36 (d, 3H, *J* = 7.3 Hz), 3.75 (d, 1H, *J* = 9.3 Hz), 3.88 (s, 3H), 3.94 (dq, 1H, *J* = 4.6, 7.3 Hz), 4.15 (apparent dq, 2H, *J* = 3.2, 7.1 Hz), 4.36 (dd, 1H, *J* = 4.6, 9.3 Hz), 6.92-6.99 (m, 2H), 7.90-7.97 (m, 2H); $^{13}$C NMR ***syn*** ($CDCl_3$) δ = 12.3, 14.0, 43.7, 55.4, 61.8, 71.7, 113.9, 128.5, 130.7, 163.7, 173.1, 200.4; ***anti*** ($CDCl_3$) δ = 14.0, 14.6, 43.2, 55.5, 61.4, 73.4, 113.9, 128.7, 130.8, 163.8, 173.2, 201.9; IR (neat) ***syn*** 3477, 2979, 2935, 2850, 1730, 1670, 1600, 1573, 1510, 1463, 1420, 1308, 1261, 1173, 1125, 1027, 976, 843, 770, 604; ***anti*** 3478, 2979, 2941, 2843, 1738, 1671, 1599, 1580, 1510, 1457, 1419, 1370, 1308, 1257, 1216, 1172, 1092, 1026, 974, 841 cm$^{-1}$; HRMS (FAB); Exact mass calcd for $C_{14}H_{19}O_5$ $[M+H]^+$, 267.1232. Found 267.1232.; HPLC, Daicel Chiralcel ADH, hexane/$^i$PrOH = 4/1, flow rate = 0.2 mL/min : $t_R$ = 60.5 min (2*R*, 3*R*), $t_R$ = 65.4 min (2*S*, 2*S*), $t_R$ = 75.2 min (2*R*, 3*S*), $t_R$ = 78.9 min (2*S*, 3*R*).



**(2*S*)-4-(4-Chloro-phenyl)-2-hydroxy-3-methyl-4-oxo-butyric acid ethyl ester ( *syn/anti* mixture):** $^1$H NMR ***syn*** ($CDCl_3$) δ = 1.26 (t, 3H, *J* = 7.0 Hz), 1.28 (d, 3H, *J* = 7.0 Hz), 3.27 (brs, 1H), 3.87 (dq, 1H, *J* = 4.4, 7.0 Hz), 4.25 (q, 2H, *J* = 7.0 Hz), 4.55 (d, 1H, *J* = 4.4 Hz), 7.40-7.55 (m, 2H), 7.84-7.97 (m, 2H); ***anti*** ($CDCl_3$) δ = 1.21 (t, 3H, *J* = 7.1 Hz), 1.34 (d, 3H, *J* = 7.1 Hz), 3.53 (d, 1H, *J* = 8.2 Hz), 3.91 (dq, 1H, *J* = 5.0, 7.1 Hz), 4.08-4.24 (m, 2H), 4.38 (dd, 1H, *J* = 5.0, 8.2 Hz), 7.42-7.52 (m, 2H), 7.80-7.95 (m, 2H); $^{13}$C NMR ***syn*** ($CDCl_3$) δ = 12.1, 14.0, 44.4, 62.0, 71.5, 129.0, 129.8, 134.1, 139.7, 173.1, 200.3; ***anti*** ($CDCl_3$) δ = 13.9, 14.0, 44.1, 61.6, 73.0, 129.0, 129.8, 134.3, 139.9, 173.0, 201.8; IR (neat) ***syn*** 3485, 2982, 2938, 1730, 1682, 1589, 1571, 1488, 1455, 1401, 1217, 1132, 1092, 1013, 977, 843, 758, 692, 533, 478; ***anti*** 3478, 3092, 2982, 2935, 1738, 1686, 1589, 1455, 1402, 1255, 1208, 1144, 1092, 1022, 976, 842, 751, 527 cm$^{-1}$; HRMS (FAB); Exact mass calcd for $C_{13}H_{16}ClO_4$ $[M+H]^+$, 271.0737. Found 271.0745.; HPLC, Daicel Chiralcel AS, hexane/$^i$PrOH = 4/1, flow rate = 0.5 mL/min : $t_R$ = 15.1 min (2*S*, 3*S*), $t_R$ = 16.6 min (2*S*, 3*R*), $t_R$ = 21.4 min (2*R*, 3*S*), $t_R$ = 23.9 min (2*R*, 3*R*).

**<Example 8>**

**A reaction was performed in a same manner as in Example 7 except that various types of enecarbamates as shown in Table 9 were used. In Table 9, yield (%), a syn/anti ratio, and ee (%) of a reaction product are shown. In Table 10, identification values of 8-1/8-2 and 8-3/8-4 of the reaction products are shown.**

**It was confirmed that, in a same manner as in Example 7, an anti-adduct and a syn-adduct were obtained from an E-body and a Z-body at high diastereoselectivity and high enantioselectivity, respectively.**

**Table 9**

| No. | $R^2$ | $R^3$ | $R^4$-$R^5$ | Yield (%) | Syn/anti | ee (%) |
|---|---|---|---|---|---|---|
| 8-1 | BnO | Ph | Et, H (E) | 90 | 1/99 | 98 |
| 8-2 | BnO | Ph | H, Et (Z) | 92 | 99/1 | 98 |
| 8-3 | BnO | Et | Me, H (E) | 83 | 3/97 | 97 |
| 8-4 | BnO | Et | H, Me (Z) | 89 | 92/8 | 98 |

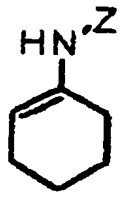
## Table 10

**(2*S*)-3-Benzoyl-2-hydroxy-pentanoic acid ethyl ester ( *syn/anti* mixture)**: $^1$H NMR *syn* ($CDCl_3$) δ = 0.93 (t, 3H, *J* = 7.5 Hz), 1.19 (t, 3H, *J* = 7.1 Hz), 1.70-2.05 (m, 2H), 3.18 (brs, 1H), 3.83 (dt, 1H, *J* = 5.3, 8.3 Hz), 4.19 (q, 2H, *J* = 7.1 Hz), 4.51 (d, 1H, *J* = 5.3 Hz), 7.42-7.54 (m, 2H), 7.54-7.62 (m, 1H), 7.90-8.02 (m, 2H); ***anti*** ($CDCl_3$) δ = 1.04 (t, 3H, *J* = 7.6 Hz), 1.15 (t, 3H, *J* = 7.1 Hz), 1.80-1.95 (m, 2H), 3.70 (d, 1H, *J* = 9.5 Hz), 3.83 (dt, 1H, *J* = 4.2, 7.1 Hz), 4.09 (q, 2H, *J* = 7.1 Hz), 4.43 (dd, 1H, *J* = 4.2, 9.5 Hz), 7.46-7.52 (m, 2H), 7.56-7.63 (m, 1H), 7.88-7.95 (m, 2H); $^{13}$C NMR ***syn*** ($CDCl_3$) δ = 12.0, 13.9, 21.3, 51.2, 61.9, 71.1, 128.3, 128.6, 133.2, 137.0, 173.6, 201.5; ***anti*** ($CDCl_3$) δ = 12.0, 13.9, 22.3, 50.1, 61.4, 71.3, 128.3, 128.7, 133.5, 136.6, 173.4, 203.9; IR (neat) ***syn*** 3477, 2972, 2876, 1738, 1675, 1596, 1447, 1372, 1255, 1220, 1118, 1023, 931, 849, 779, 701; ***anti*** 3485, 3062, 2966, 2941, 2875, 1738, 1682, 1596, 1579, 1448, 1368, 1268, 1208, 1134, 1100, 1028, 914, 849, 785, 699 cm$^{-1}$; HRMS (FAB); Exact mass calcd for $C_{14}H_{19}O_4$ $[M+H]^+$, 251.1283. Found 251.1277.; HPLC, Daicel Chiralcel AS, hexane/$^i$PrOH = 4/1, flow rate = 0.5 mL/min : $t_R$ = 13.7 min (2*S*, 3*S*), $t_R$ = 15.3 min (2*S*, 3*R*), $t_R$ = 17.6 min (2*R*, 3*R*), $t_R$ = 23.1 min (2*R*, 3*S*).

**(2*S*)-2-Hydroxy-3-methyl-4-oxo-hexanoic acid ethyl ester ( *syn/anti* mixture)**: $^1$H NMR ***syn*** ($C_6D_6$) δ = 0.89 (t, 3H, *J* = 7.1 Hz), 0.99 (d, 3H, *J* = 7.2 Hz), 1.97-2.08 (m, 2H), 2.70 (dq, 1H, *J* = 4.9, 7.2 Hz), 3.39 (d, 1H, *J* = 6.7 Hz), 3.80-4.00 (m, 2H), 4.11 (dd, 1H, *J* = 4.9, 6.7 Hz); ***anti*** ($C_6D_6$) δ = 0.87 (t, 3H, *J* = 7.1 Hz), 0.93 (t, 3H, *J* = 7.3 Hz), 1.02 (d, 3H, *J* = 7.2 Hz), 1.95-2.22 (m, 2H), 2.65 (dq, 1H, *J* = 4.4, 7.2 Hz), 3.05-3.23 (m, 1H), 3.80-4.00 (m, 2H), 4.38-4.47 (m, 1H); $^{13}$C NMR ***syn*** ($CDCl_3$) δ = 7.58, 12.8, 14.0, 34.6, 49.4, 61.3, 73.0, 173.5, 211.3; ***anti*** ($C_6D_6$) δ = 7.7, 11.0, 14.0, 34.0, 49.5, 61.6, 71.7, 173.7, 209.9; IR (neat) ***syn*** 3484, 2981, 2940, 1739, 1716, 1459, 1409, 1375, 1268, 1209, 1108, 1066, 1025, 975, 862, 808, 748; ***anti*** 3488, 2981, 2940, 1733, 1716, 1459, 1373, 1218, 1145, 1025, 977, 862, 800, 752 cm$^{-1}$; HRMS (FAB); Exact mass calcd for $C_9H_{17}O_4$ $[M+H]^+$, 189.1127. Found 189.1120.;

**<Example 9>**

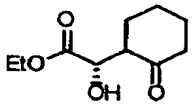
**A reaction was performed in a same manner as in Example 7 except that an enecarbamate represented by the following formula as an enamide:**



(wherein Z represents benzyloxycarbonyl group)

Thus, a next compound was obtained at a yield of 85% with a syn/anti of 16/84 and 94 ee (%).

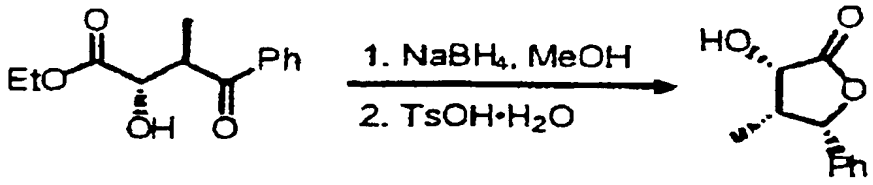
Table 11



**(1*S*)-Hydroxy-(2-oxo-cyclohexyl)-acetic acid ethyl ester ( *syn/anti* mixture)**: $^1$H NMR ***anti*** ((1*S*, 1'*R*), tentatively assignment) ($C_6D_6$) δ = 0.95 (t, 3H, *J* = 7.1 Hz), 0.94-1.20 (m, 2H), 1.30-1.42 (m, 2H), 1.56-1.84 (m, 3H), 2.02-2.12 (m, 1H), 2.60-2.70 (m, 1H), 3.35 (d, 1H, *J* = 7.2 Hz), 3.84 (dd, 1H, *J* = 3.2, 7.2 Hz), 4.02 (dq, 2H, *J* = 1.9, 7.1 Hz); **distingishable *syn* peaks** δ = 0.88 (t, 3H, *J* = 7.1 Hz), 2.12-2.21 (m, 1H), 2.48-2.57 (m ,1H), 2.94 (d, 1H, *J* = 5.0 Hz), 4.60 (dd, 1H, *J* = 3.2, 5.0 Hz); $^{13}$C NMR ***anti*** ($CDCl_3$) δ = 14.1, 24.8, 26.9, 30.1, 42.0, 53.7, 61.6, 71.1, 173.4, 211.2; **distinguishable *syn* peaks** δ = 14.2, 24.6, 27.1, 41.9, 53.8, 61.7, 69.2, 173.6, 210.4; HRMS (FAB); Exact mass calcd for $C_{10}H_{17}O_4$ $[M+H]^+$, 201.1127. Found 201.1127.;

<Example 10>

From the reaction product obtained in Example 7, an optically active α-hydroxy-γ-lactone was synthesized in accordance with the following reaction formulae:




Namely, MeOH (1.0 ml) of the anti-body (45.6 mg, 0.193 mmol) of the reaction product was added with $NaBH_4$ (14.6 mg, 0.39 mmol) at 0°C, stirred for

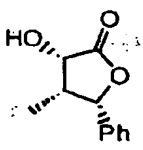
**10 minutes, added with acetone, stirred further for 5 minutes and, then, added with a saturated aqueous solution of $NH_4Cl$.**

**The resultant mixture was subjected to extraction by using $CH_2Cl_2$, dried and, then, a solvent was evaporated. Thereafter, the resultant $CH_2Cl_2$ solution (1 ml) was added with $TsOH \cdot H_2O$ and, then, stirred for 13.5 hours at room temperature.**

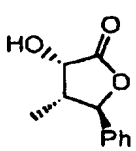
**The resultant reaction product was added with a saturated aqueous solution of $NaHCO_3$, subjected to extraction by using $CH_2Cl_2$, dried and, then, subjected to a solvent-evaporation treatment. The resultant crude product was purified by using silica gel chromatography. As a product, the lactone compound as shown in the above-described reaction formulae and an epi-body thereof (ratio: 55/45) were obtained as a diastereomer mixture in an amount of 19.8 mg at a yield of 53%.**

**In Table 12,identification values of the products are shown below.**

**Table 12**



**(3*S*, 4*R*, 5*S*)-3-Hydroxy-4-methyl-5-phenyl-dihydro-furan-2-one** Mp: 150-151 °C; $^1H$ NMR ($CDCl_3$) $\delta$ = 0.65 (d, 3H, $J$ = 7.3 Hz), 2.75 (brs, 1H), 2.98-3.08 (m, 1H), 4.79 (d, 1H, $J$ = 6.8 Hz), 5.57 (d, 1H, $J$ = 4.6 Hz), 7.25-7.30 (m, 2H), 7.30-7.38 (m, 1H), 7.38-7.45 (m, 2H); $^{13}C$ NMR ($CDCl_3$) $\delta$ = 7.4, 41.1, 72.1, 80.2, 125.2, 128.2, 128.6, 135.1, 177.0; IR (neat) 3443, 2963, 1758, 1452, 1414, 1294, 1194, 1148, 1051, 956, 754, 701, 622, 478 $cm^{-1}$; HRMS (FAB); Exact mass calcd for $C_{11}H_{13}O_3$ $[M+H]^+$, 193.0865. Found 193.0872.;

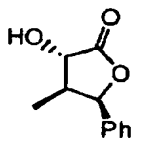


**(3*S*, 4*R*, 5*R*)-3-Hydroxy-4-methyl-5-phenyl-dihydro-furan-2-one (epi- ):** $^1H$ NMR ($CDCl_3$) $\delta$ = 1.22 (d, 3H, $J$ = 7.1 Hz), 2.62 (tq, 1H, $J$ = 5.1, 6.8 Hz), 2.86 (brs, 1H), 4.47 (d, 1H, $J$ = 6.8 Hz), 5.26 (d, 1H, $J$ = 5.1 Hz), 7.20-7.45 (m, 5H); $^{13}C$ NMR ($CDCl_3$) $\delta$ = 10.8, 43.2, 69.7, 85.8, 125.3, 128.6, 128.8, 137.7, 176.9; IR (neat) 3430, 3039, 2924, 2857, 1772, 1455, 1275, 1202, 1143, 1093, 986, 889, 805, 742, 702 $cm^{-1}$; HRMS (FAB); Exact mass calcd for $C_{11}H_{13}O_3$ $[M+H]^+$, 193.0865. Found 193.0864.;

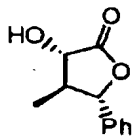
**In a same manner as described above, by using the syn-body of the product in Example 7 as a raw material, a lactone compound and an epi-body thereof (ratio: 86/14) were obtained at a yield of 84%.**

**In Table 13, identification values of the products are shown below.**

**Table 13**



**(3*S*, 4*S*, 5*R*)-3-Hydroxy-4-methyl-5-phenyl-dihydro-furan-2-one** : $^1$H NMR ($CDCl_3$) δ = 0.87 (d, 3H, *J* = 7.0 Hz), 2.70-2.92 (m, 1H), 3.18 (brs, 1H), 4.24 (d, 1H, *J* = 9.9 Hz), 5.63 (d, 1H, *J* = 8.1 Hz), 7.05-7.18 (m, 2H), 7.30-7.45 (m, 3H); $^{13}$C NMR ($CDCl_3$) δ = 13.3, 42.1, 72.2, 82.4, 125.7, 128.5, 128.6, 135.5, 177.5; IR (neat) 3362, 2970, 1776, 1455, 1334, 1184, 1145, 1096, 991, 897, 755, 701, 464 cm$^{-1}$; HRMS (FAB); Exact mass calcd for $C_{11}H_{13}O_3$ $[M+H]^+$, 193.0865. Found 193.0872.;



**(3*S*, 4*S*, 5*S*)-3-Hydroxy-4-methyl-5-phenyl-dihydro-furan-2-one (epi-)**: $^1$H NMR ($CDCl_3$) δ = 1.24 (d, 3H, *J* = 6.4 Hz), 2.41 (tq, 1H, *J* = 6.4, 10.6 Hz), 3.24 (brs, 1H), 4.25 (d, 1H, *J* = 11.0 Hz), 4.87 (d, 1H,

【Title of the document】 Abstract

【Abstract】

【Problem】 The present invention has an object of providing a method of an enantioselective nucleophilic addition reaction to an aldehyde group which enables an asymmetric synthesis of an α-hydroxy-γ-keto acid compound, an α-hydroxy-γ-amino acid compound or the like which is useful as a raw material or a synthesis intermediate for producing a pharmaceutical preparation, an agricultural chemical, a fragrance, a functional polymer or the like and, further, as an application thereof, a novel synthesis method of the α-hydroxy-γ-keto acid ester or the like.

【Means for resolution】 There is provided a method of an enantioselective nucleophilic addition reaction of enamide which is a method of a nucleophilic addition reaction of an enamide compound accompanied by generation of a hydroxyl group (-OH) to an aldehyde group (-CHO) of an aldehyde compound and which is characterized by allowing the reaction to be performed in the presence of a chiral copper catalyst.

【Selected Figure】 None

PCT/JP05/001281

2005 04 25

# PATENT COOPERATION TREATY

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JAPON

| | |
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| Date of mailing *(day/month/year)*<br>13 April 2005 (13.04.2005) | |
| Applicant's or agent's file reference<br>05-F-008PCT | **IMPORTANT NOTIFICATION** |
| International application No.<br>PCT/JP05/001281 | International filing date *(day/month/year)*<br>24 January 2005 (24.01.2005) |
| International publication date *(day/month/year)* | Priority date *(day/month/year)*<br>23 January 2004 (23.01.2004) |
| Applicant<br>JAPAN SCIENCE AND TECHNOLOGY AGENCY et al | |

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2. *(If applicable)* The **letters "NR"** appearing in the right-hand column denote **a priority document which, on the date of mailing of this Form, had not yet been received by the International Bureau** under Rule 17.1(a) or (b). Where, under Rule 17.1(a), the priority document must be submitted by the applicant to the receiving Office or the International Bureau, but the applicant fails to submit the priority document within the applicable time limit under that Rule, **the attention of the applicant is directed** to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

3. *(If applicable)* **An asterisk (*)** appearing next to a date of receipt, in the right-hand column, denotes **a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b)** (the priority document was received after the time limit prescribed in Rule 17.1(a) or the request to prepare and transmit the priority document was submitted to the receiving Office after the applicable time limit under Rule 17.1(b)). Even though the priority document was not furnished in compliance with Rule 17.1(a) or (b), the International Bureau will nevertheless transmit a copy of the document to the designated Offices, for their consideration. In case such a copy is not accepted by the designated Office as the priority document, Rule 17.1(c) provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

| Priority date | Priority application No. | Country or regional Office or PCT receiving Office | Date of receipt of priority document |
|---|---|---|---|
| 23 January 2004 (23.01.2004) | 2004-016408 | JP | 10 March 2005 (10.03.2005) |
| 27 August 2004 (27.08.2004) | 2004-249251 | JP | 10 March 2005 (10.03.2005) |


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